

rejection is set forth in the Office Action. Applicant respectfully requests that claim 48 be examined on the merits.

II. The Examiner's Rejections

The Examiner has made the following rejections under 35 U.S.C. §103(a):

Claims 31-34, 43-45 and 59-61 stand rejected as allegedly unpatentable over Teale in view of Williamson for the reasons given at pages 2-3 of the Office Action of February 5, 1998, as supplemented in the Final Office Action of July 21, 1998;

Claims 35 and 51 stand rejected as allegedly unpatentable over Teale in view of Wilhelm and Williamson for the reasons given at page 3 of the Office Action of February 5, 1998, as supplemented in the Final Office Action of July 21, 1998;

Claims 36-39, 47, 52-55, 63 and 64 stand rejected as allegedly unpatentable over Yu in view of Williamson for the reasons given at pages 3-4 of the Office Action of February 5, 1998, as supplemented in the Final Office Action of July 21, 1998; and

Claims 45, 46, 61 and 62 stand rejected as unpatentable over Teale in view of Ahluwalia for the reasons found at page 5 of the Office Action of February 5, 1998, as supplemented in the Final Office Action of July 21, 1998.

The above rejections are traversed for the reasons set forth below and in the response of May 4, 1998, which is incorporated by referenced herein.

III. Teachings of the Prior Art

Teale in view of Williamson

Teale relates to a treatment of systemic inflammatory response syndrome (SIRS). The treatment uses a combination of a corticosteroid as an anti-inflammatory agent and a preferential inhibitor of inducible nitric oxide synthase (iNOS) as an anti-hypotension agent (see Teale, page 2, line 56 -page 3, line 11) . Teale is quite clear that the corticosteroid is the anti-inflammatory —and the iNOS inhibitor is the anti-hypotension agent. Thus, there is no explicit teaching in Teale and it would not have been obvious, relying on the teaching of Teale, to use an iNOS inhibitor as an anti-inflammatory agent.

Teale teaches that the combination of an iNOS inhibitor and an anti-inflammatory agent produces a synergistic effect, permitting smaller, and therefore less toxic, doses of the corticosteroid anti-inflammatory in the treatment of a very serious type of inflammation (see Teale, page 2, lines 26-57). Teale does not teach or suggest the use of iNOS inhibitor for the treatment of inflammation —only that it can possibly exhibit a synergistic effect with a known anti-inflammatory agent. Further, neither does Teale teach or suggest the use of iNOS inhibitor in connection with products which are capable of causing an irritant effect. In fact, Teale does not teach any connection between a product causing an irritant effect and the type of inflammation for which Teale suggests combining an iNOS inhibitor with a known anti-inflammatory drug. The

combination of a product causing an irritant effect and iNOS inhibitor is central to the claims, and that combination is not taught by Teale or any other prior art of record.

Moreover, Teale relates to a pharmaceutical composition comprising an iNOS inhibitor as opposed to constitutive nitric oxide synthase (cNOS) for the therapeutic treatment of the pathological consequences of SIRS (see Teale, abstract). In contrast, claim 43 recites a composition which comprises a cNOS inhibitor, that is, in the words of Applicant's specification at page 7, lines 21-24: "inhibitors which inhibit the constitutive NO-synthase equally or more compared with the inducible NO-synthase." Teale is completely silent with respect to a composition comprising a cNOS inhibitor; hence, and it could not have been obvious to select a cNOS inhibitor by relying on Teale, because Teale teaches an iNOS inhibitor to the apparent exclusion of the cNOS inhibitor. See especially, Teale, page 2, lines 19-21.

Further, Teale relates to a "treatment" of inflammation, and more specifically to the treatment of SIRS. By "treatment" is meant the use of a composition containing an NO synthase inhibitor to address the pathological consequences of SIRS. As Applicant pointed out in the previous amendment, the concept of treating inflammation is entirely different from the concept of providing a component in a cosmetic composition so that irritation does not begin to occur. Nothing in Teale or any of the other references suggests such a combination. It would not have been obvious to modify a composition for treatment of inflammation by adding components to the composition which cause irritation or inflammation. Indeed, Teale teaches away from such a combination.

The Office Action cites Williamson in an attempt to remedy the deficiencies of Teale. Williamson, according to the Office Action, "recognizes several physical, chemical and biological agents capable of causing inflammation of the skin." However, none of these agents appear to be a cosmetic or pharmaceutical product. Williamson, like Teale, fails to suggest the combination of irritant ingredients with a constitutive NO synthase inhibitor. Accordingly, Williamson does not appear to add anything of substance to Teale. In view of the foregoing, these references together are insufficient to make a *prima facie* case of obviousness against any of the pending claims. Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Teale in view of Wilhelm and Williamson

Neither Wilhelm nor Williamson remedy the substantial defects of Teale, which is described above in detail, as a primary reference. While Wilhelm teaches that certain surfactants can cause irritation, it does not teach or suggest that surfactants cause irritation by producing nitric oxide. The Office Action combines Wilhelm with Williamson and Teale for the proposition that "one can conclude from the teachings of Wilhelm and Williamson that surfactants may lead to contact dermatitis by way of producing nitric oxide." However, neither Williamson nor Wilhelm suggests that the "dermatitis" in both references is the same, or that all dermatitis is caused by nitric oxide—which, of course, it does not. To the contrary, Williamson speaks only of "dermatitis" (an extremely broad term) and not "contact dermatitis," which is the term used by Wilhelm. Williamson

never mentions surfactants. The only teaching that cosmetics contain irritants, the effect of which can be ameliorated by the addition of cNOS inhibitors, appears in the present specification. The combination of Wilhelm with Williamson as secondary references in combination with Teale is thus based on impermissible hindsight reconstruction, and accordingly the rejection under 35 U.S.C. 103(a) should be withdrawn.

Yu in view of Williamson

Yu discloses the use of α -hydroxy acids and various other compounds for the treatment of various skin conditions (page 2, lines 1-7). In its discussion of the prior art, Yu describes that the low pH of the subject compounds causes skin irritation (page 2, lines 37-49). Yu discloses that this problem is solved by providing certain amphoteric compositions comprising the subject compounds (page 3, lines 16-30). The Office Action combines Yu with Williamson, arguing that since Yu teaches that the presently claimed compounds cause irritation, and Williamson teaches that inflammation can be treated with NO synthase inhibitors, it allegedly would have been obvious to include a NO synthase inhibitor, disclosed in Williamson, in the composition of Yu. The combination is flawed in several respects.

First, it is quite clear from Yu that the irritation caused by the subject compounds is due to the low pH of those compounds. Yu does not suggest that the irritation is caused by nitric oxide. Therefore, it would not have been obvious at all, from either Yu or Williamson, to introduce a NO synthase inhibitor into the Yu composition. Second,

Yu provides its own solution for the irritation caused by the low pH of the subject compounds —the addition of certain amphoteric compositions. Therefore, by teaching a solution to the problem of skin irritation other than using a NO synthase inhibitor, Yu teaches away from the combination with Williamson. Finally, as with all of the rejections of record, the bare recognition that iNOS inhibitors can be used in connection with the treatment of certain types of inflammation does not amount to a suggestion to include NO synthase inhibitor in a cosmetic composition. Accordingly, this rejection under § 103(a) should be withdrawn.

Teale in view of Ahluwalia

Finally, the Office Action has rejected claims 45, 46, 61 and 62 over Teale in view of Ahluwalia. As with the other prior art cited in the Office Action, Ahluwalia does not remedy Teale's deficiencies. As previously argued by the Applicant, Ahluwalia teaches the use of a NO synthase inhibitor for the removal of hair. The Office Action does not set forth any cogent arguments why one of ordinary skill in the art would have incorporated these compounds into the composition of Teale, much less into the cosmetic or pharmaceutical composition of the present invention. Accordingly, Applicant respectfully requests that the rejection under § 103(a) be withdrawn.

IV. Response to Arguments of the Office Action

Applicant does not agree with the Office Action's statement on page 2 of the Office Action: "the claims in the instant invention are directed towards a composition containing a cosmetic or pharmaceutical and **not to the cutaneous irritant effect**" (emphasis added). The present claim limitation "capable of causing a cutaneous irritant effect" has a definite meaning as used in the specification and cannot be ignored. This limitation is an integral part of a claim, and must be considered equally with the other claim limitations. In the present case, the importance of this functional limitation to the invention is also shown in the dependent claims, where components which are capable of causing a cutaneous irritant effect are individually claimed. The combination of a component which causes an irritant effect and a NO synthase inhibitor which counteracts that effect is not found in the prior art. Therefore, Applicant submits that the various rejections under 35 U.S.C. § 103(a) should be withdrawn because the cited references fail to disclose or suggest the combination of an irritation-causing compound and a NO synthase inhibitor compound in the same cosmetic composition.

Applicant disagrees with the Office Action's statements in support of the combination of Yu and Williamson, that is, one of ordinary skill in the art would have inferred that the skin irritation described in Yu was caused by a "caustic substance" as that term is understood in Williamson at col. 3, line 11, and that the irritation was due to NO synthase. "Caustic," in the sense used by Williamson, means "capable of destroying or eating away by chemical action" (Webster's New Collegiate Dictionary,

Sixth Ed. (1979)). In the amounts described by Yu, the subject compounds may be irritating to certain individuals, but they are hardly caustic. Thus, neither Yu nor Williamson provides a basis for making the combination, especially because Yu discloses an entirely different means for dealing with skin irritation caused by the subject compounds.

V. Conclusion

To establish a *prima facie* case of obviousness, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. The combination put together in this way must read on the claimed invention. See *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). The various combinations presented in the Office Action fail to teach all of the limitations of the present claims, and are based entirely on hindsight.

Further, with regard to claims 43 and 59, neither Teale, nor any of the other references, taken alone or in combination, suggest substituting a cNOS inhibitor for the iNOS inhibitor of Teale. None of the references teach including a cNOS inhibitor in any composition at all, much less including such an NO synthase inhibitor in a pharmaceutical or cosmetic composition which includes a component capable of causing cutaneous irritation.


The cited references are further deficient because they fail to identify a reasonable motivation found in the prior art, or known to one of ordinary skill in the art, that would have led to a combination that would result in the currently pending claims. The critical teaching missing from all of the references cited by the Examiner is the teaching that a cosmetic composition containing a skin irritating component can be advantageously improved (e.g., less irritating when applied to the skin, etc.) by adding a NO synthase inhibitor. Without that teaching, or at least something that would have made such a combination obvious to one of ordinary skill in the art, the cited references do not support a *prima facie* case of obviousness.

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of the pending claims and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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